

Manuscript Details

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Abstract

Over the last three decades there has been an accumulation of Magnetic Resonance Imaging (MRI) studies reporting that aberrant functional networks may underlie cognitive deficits and other symptoms across a range of psychiatric diagnoses. The use of pharmacological MRI and 1H-Magnetic Resonance Spectroscopy (1H-MRS) has allowed researchers to investigate how changes in network dynamics are related to perturbed excitatory and inhibitory neurotransmission in individuals with psychiatric conditions. More recently, changes in functional network dynamics and excitatory/inhibitory (E/I) neurotransmission have been linked to early childhood trauma, a major antecedents for psychiatric illness in adulthood. Here we review studies investigating whether perturbed network dynamics seen across psychiatric conditions are related to changes in E/I neurotransmission, and whether such changes could be linked to childhood trauma.

Keywords	Keywords: Psychiatric disorders, Schizophrenia, Anxiety, Trauma, fMRI, Cortical Networks, Connectivity, Excitatory transmitters, Inhibitory transmitters
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Suggested reviewers	Jason Moser, Ulrich Ettinger, Stefan Borgwardt, Simon McCarthy-Jones, Matthijs Bossong

Submission Files Included in this PDF

File Name [File Type]

R1_cover_letter.docx [Cover Letter]

Rebuttal_Letter_300119.docx [Response to Reviewers]

Allen_et_al_Highlights.docx [Highlights]

ABSTRACT.docx [Abstract]

ALLEN_et_al_NBR_Jan2019_r1.b.docx [Manuscript File]

Table 1 _MRS-fMRI studies .docx [Table]

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article



30th January 2019

Dear Dr. Easton,

Please find attached our revised manuscript "*Extrinsic and default mode networks in psychiatric conditions: Relationship to excitatory-inhibitory transmitter balance and early trauma*". We thank you for inviting us to resubmit our manuscript with minor revisions. These are outlined in the Rebuttal Letter attached to the resubmission. We hope these revisions are satisfactory and we look forward to hearing from you soon.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'P Allen'.

Paul Allen BSc MSc PhD FHEA
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RE: Revision requested for NEUBIOREV_2018_653

Dear Dr Easton,

We would first like to thank you for inviting us to resubmit our manuscript to NBR. We have addressed each of the reviewers' comments below and amended the manuscript accordingly. Changes to the manuscript have been highlighted in the revised version attached. We hope that these amendments are satisfactory and we look forward to hearing from you shortly.

Yours sincerely,

Paul Allen

Reviewer 1:

"Unless there is a compelling reason why a systematic review can't be done, I would strongly recommend to use systematic review methods and to organise the review accordingly."

Response: We understand the concerns the Reviewer may have regarding a systematic review. However, as stated in the Introduction (Page 5), the aim of the paper was to conduct a "selective review" with the goal of developing a framework in which to advance a hypothesis of cortical network interaction, and corresponding neurotransmitter interaction and imbalances, as a mechanistic model for the understanding of mental disorders. This has been clarified in an amendment on page 5.

By conducting this selective review we aim to advance a hypothesis of cortical network interaction, and corresponding neurotransmitter interaction and imbalances due to childhood trauma as a mechanistic model for cognitive dysfunction across psychiatric disorders.

Thus, a systematic review was never intended, and would go beyond the scope of the submitted work. Importantly, it could also be argued that providing a systematic review at this stage of the development of this new research field may be premature, because of very few studies, which may lead to misleading conclusions, such that this should perhaps wait until more empirical work has been conducted.

"Tables presenting details of the discussed studies would help the reader to get a brief overview."

Response: We thank the reviewer for suggesting adding a table, summarising the results of some of the studies. As explained previously, there is currently a lack of empirical work pertaining to our primary hypothesis. However, there is an emerging empirical literature reporting multimodal 1H-MRS-fMRI studies in psychiatric and psychiatric risk populations (note: a systematic review of multimodal 1H-MRS-fMRI in non-psychiatric population is provided by Duncan, et al. 2014). Thus we have added Table 1 to the manuscript which lists a number of multimodal 1H-MRS-fMRI studies in psychiatric populations. We refer to this new table in an amendment on Page 19

A systematic review of ¹H-MRS-fMRI multimodal imaging studies reporting effects of glutamate and GABA on network activation is provided by Duncan and colleagues (Duncan, et al. 2014). ¹H-MRS-fMRI multimodal imaging studies in psychiatric and psychiatric risk populations are listed in Table 1.

Reviewer 2:

"Among 142 reviewed sources only 3 publication are really recent, i.e. published in 2018. Taking into account a key importance of MRI/MRS in investigation of human brain, and accelerating rate of methodological development and, I believe it is absolutely necessary to extend/update the review with analysis of very recent publications."

Response: We have updated the review with 10 new references. These new references report on MR/MRS and brain metabolites, fMRI or network interactions studies from 2018 and 2019. Newly added references are highlighted in the references section of the manuscript and example of where new citations have been added to the main text is below (page 20). From the very recent general review on MR/MRS by Dwyer et al. (ePub Dec 2018), these references are the most recent studies available, as we can see from the literature. This is a new and emerging field of research where many already published studies are not to be expected.

These findings provide further support for E/I neurotransmitter imbalance in MDD and schizophrenia, supported by more recent studies which all report aberrant metabolite levels in schizophrenia and psychosis (Dwyer, et al. 2018; Jelen, et al. 2018; Psomiades, et al. 2018; Reid, et al. 2019; Kim, et al. 2018; Singh, et al. 2018). However, currently there is no evidence for differences in GABA levels between healthy controls and patients with bipolar or anxiety disorders (Schur, et al. 2016).

Minor:

1. *Abstract: Currently abstract rather focused on general importance of MRI for study of psychotic disorders, and on perspectives, which further methodological improvement (MRS) provides. I would suggest to include at the end of the abstract a few sentences which would summarize the authors' opinion regarding current knowledge in the field, which is, to my belief, a main goal of each review.*

Response: We agree with the reviewer that the abstract could be improved in this way and have amended the manuscript on Page 3.

"Whilst there is currently a paucity of studies relating early traumatic experiences to altered E/I balance and network function, the research discussed here lead towards a plausible mechanistic hypothesis, linking early traumatic experiences to cognitive dysfunction and symptoms mediated by E/I neurotransmitter imbalances."

The formal style of the text is especially important for such type of scientific work as a review. Thus, few imperfectness in the text must be improved:

- a. *Please take care that all abbreviations are described when used 1st time in the text: For*

example, page 18 – BOLD; page 20 – glx; page 22 – SCZ.

b. Please take care that titles of all compounds are written in the same style: For example, “ketamine” on page 19 is written with small “k”, however on page 20 with capital “K”.

c. Please make sure that all citations of original articles are made in the same style. For example, on page 33 articles of Hugdahl, Raichle et. all, and Hugdahl & Sommer are cited without providing the publication year.

Response: We thank the reviewer for drawing attention to these typographical errors. We have specifically corrected the errors listed above and others that were noticed after thorough proofreading.

Highlights:

- Interaction between Extrinsic and Default Mode Networks are perturbed in psychiatric conditions
- Perturbed network interactions underlie cognitive deficits and psychiatric symptoms
- Perturbed network interactions related to excitatory/inhibitory neurotransmitter imbalances
- Childhood trauma can affect excitatory/inhibitory neurotransmitter imbalances

ABSTRACT

Over the last three decades there has been an accumulation of Magnetic Resonance Imaging (MRI) studies reporting that aberrant functional networks may underlie cognitive deficits and other symptoms across a range of psychiatric diagnoses. The use of pharmacological MRI and ¹H-Magnetic Resonance Spectroscopy (¹H-MRS) has allowed researchers to investigate how changes in network dynamics are related to perturbed excitatory and inhibitory neurotransmission in individuals with psychiatric conditions. More recently, changes in functional network dynamics and excitatory/inhibitory (E/I) neurotransmission have been linked to early childhood trauma, a major antecedents for psychiatric illness in adulthood. Here we review studies investigating whether perturbed network dynamics seen across psychiatric conditions are related to changes in E/I neurotransmission, and whether such changes could be linked to childhood trauma. Whilst there is currently a paucity of studies relating early traumatic experiences to altered E/I balance and network function, the research discussed here lead towards a plausible mechanistic hypothesis, linking early traumatic experiences to cognitive dysfunction and symptoms mediated by E/I neurotransmitter imbalances.

**Title: Extrinsic and default mode networks in psychiatric conditions:
Relationship to excitatory-inhibitory transmitter balance and early trauma.**

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ABSTRACT

Over the last three decades there has been an accumulation of Magnetic Resonance Imaging (MRI) studies reporting that aberrant functional networks may underlie cognitive deficits and other symptoms across a range of psychiatric diagnoses. The use of pharmacological MRI and ¹H-Magnetic Resonance Spectroscopy (¹H-MRS) has allowed researchers to investigate how changes in network dynamics are related to perturbed excitatory and inhibitory neurotransmission in individuals with psychiatric conditions. More recently, changes in functional network dynamics and excitatory/inhibitory (E/I) neurotransmission have been linked to early childhood trauma, a major antecedents for psychiatric illness in adulthood. Here we review studies investigating whether perturbed network dynamics seen across psychiatric conditions are related to changes in E/I neurotransmission, and whether such changes could be linked to childhood trauma. Whilst there is currently a paucity of studies relating early traumatic experiences to altered E/I balance and network function, the research discussed here lead towards a plausible mechanistic hypothesis, linking early traumatic experiences to cognitive dysfunction and symptoms mediated by E/I neurotransmitter imbalances.

Keywords: Psychiatric disorders, Schizophrenia, Anxiety, Trauma, fMRI, Cortical Networks, Connectivity, Excitatory transmitters, Inhibitory transmitters

1. Introduction

Mental health disorders make up thirty-five per cent of non-communicable diseases and overall account for 12.3% of the total global burden of disease and this figure is expected to rise to 15% by the year 2020 (World Health Forum 2011). In England (the home country of the lead author) approximately one in six adults is already affected by a psychiatric illness (Weich, et al. 2016). Given these statistics, there is clearly a pressing need for scientists and clinicians to improve understanding of mental illness, the underlying neurobiological mechanisms and how these are affected by environmental factors such as early trauma. Critically, one of the most important research findings of the last decade is that psychiatric diagnoses should not be viewed as entirely separate entities, but rather as different points on a spectrum. This is because many risk factors, including childhood trauma and prolonged stress are shared across common psychiatric illnesses (Paus, et al. 2008). Similarly, symptom complexes, such as cognitive dysfunction and emotional dysregulation are also seen across several disorders. There is also a large overlap in risk genes for major psychiatric disorders (Psychiatric genome-wide association study 2015).

Functional neuroimaging, in particular functional magnetic resonance imaging (fMRI), has been used for several decades and has helped to shed light on the workings of the most complex organ known to humankind: the human brain. Moreover, functional neuroimaging, in combination with cognitive and pharmacological science, has been an important vehicle for the development of mechanistic models of psychiatric illness (Cuthbert and Insel 2013; Badcock and Hugdahl 2014). As we have learnt more about the functioning of the human brain, neuroscientists have developed a systems approach by grouping human brain regions into functional networks (Power, et al.

2011). There is increasing evidence that dysfunction within and between these functional networks is associated with psychopathology, particularly cognitive impairments that are seen across a range of psychiatric diagnoses (i.e. schizophrenia, anxiety and affective disorders; (Anticevic, et al. 2012; Skudlarski, et al. 2010; Sylvester, et al. 2012). Here, we will first discuss evidence that network dysfunction and imbalance are seen across a range of psychiatric diagnoses and in particular, may be related to cognitive impairments that are common in psychiatric conditions. This selective review will then consider if functional network imbalance is a consequence of altered excitatory and inhibitory (E/I) neurotransmission (governed by glutamate and gamma-aminobutyric acid (GABA)), and how E/I imbalances (Jardri, et al. 2016) could result from early life trauma, a factors known to strongly predict adult psychiatric illness (Paus, et al. 2008). By conducting this selective review we aim to advance a hypothesis of cortical network interaction, and corresponding neurotransmitter interaction and imbalances due to childhood trauma as a mechanistic model for cognitive dysfunction across psychiatric disorders.

2. Networks in the brain

Functional networks are collections of brain regions in which activity tends to increase or decrease together, both at rest and during cognitive tasks (Sylvester, et al. 2012). Activity in each of these different functional networks is believed to implement unique aspects of human cognition. These networks are typically defined by functional connectivity (i.e. activation correlations) at rest and/or during cognitively demanding tasks (Sylvester, et al. 2012; Fox, et al. 2005). Moreover, activity in some functional networks is believed to be anti-correlated, meaning that as activity in one network increases in response to a particular behavioural demand, activity in another network may be down-regulated (Fox, et al. 2005). Functional

networks in humans include, but are not limited to, the cingulo-opercular network, fronto-parietal network or dorsal attentional network, ventral attentional network, default mode network, sensorimotor, visual and auditory networks (Sylvester, et al. 2012; Li, et al. 2018; Mills, et al. 2018; Mitra and Raichle 2018). In this review we will focus largely on activity and interactions between two functional networks. A task-dependent network that supports cognitively demanding tasks, often referred to as the fronto-parietal network, executive or extrinsic mode network (Hugdahl, et al. 2015). The second network is the Default Mode Network, which is usually up-regulated during periods of task absence (Fox, et al. 2005).

2.1 The Extrinsic Mode Network (EMN)

The EMN is conceptually similar to the multiple demand system (Duncan and Owen 2000), the fronto-parietal network (Dosenbach, et al. 2007), task-related/control network (Corbetta, et al. 2008). Similar to these networks, the EMN includes bilateral anterior portions of the dorsolateral prefrontal cortex (DLPFC) and the bilateral inferior parietal lobule. The EMN is usually implicated in top-down attentional control during cognitively demanding tasks and is similar in spatial anatomy to the dorsal attention and cognitive control networks (Corbetta, et al. 2008; Hugdahl, et al. 2015). Importantly, EMN activation is seen during different cognitive functions and tasks used across a range of studies e.g. spatial working memory, verbal working memory, response inhibition, Stroop colour-words task, arithmetic task and oddball detection tasks. All of these tasks activate a similar network of regions with a fronto-parietal cortical distribution. Hugdahl et al. (2015) performed a conjunction analysis across functional MRI data related to these tasks and revealed a common network including the bilateral prefrontal cortex, the left inferior parietal lobe, angular gyrus,

middle occipital gyrus, anterior cingulate gyrus and supplementary motor area, caudate nucleus, and the right inferior temporal gyrus, thalamus, precuneus and hippocampus. This network was labelled the Extrinsic Mode Network (EMN). Despite the commonality of this spatial network across tasks, the only obvious commonality across the cognitive tasks used was that they all required allocation of extrinsic intellectual capacity. Hugdahl, et al. (2015) suggest the EMN as an umbrella term for networks that share a common activation pattern, and which are up-regulated during task processing independently of the specific cognitive task structure. The EMN is hypothesized as a dynamic network that may show individual differences in core EMN regions between individuals to the same tasks, depending on the amount of previous experiences with the task. The EMN is therefore a marker of the brain's extrinsic activity and is not simply responding to increased task difficulty, as this would be task-specific, while the EMN is task non-specific.

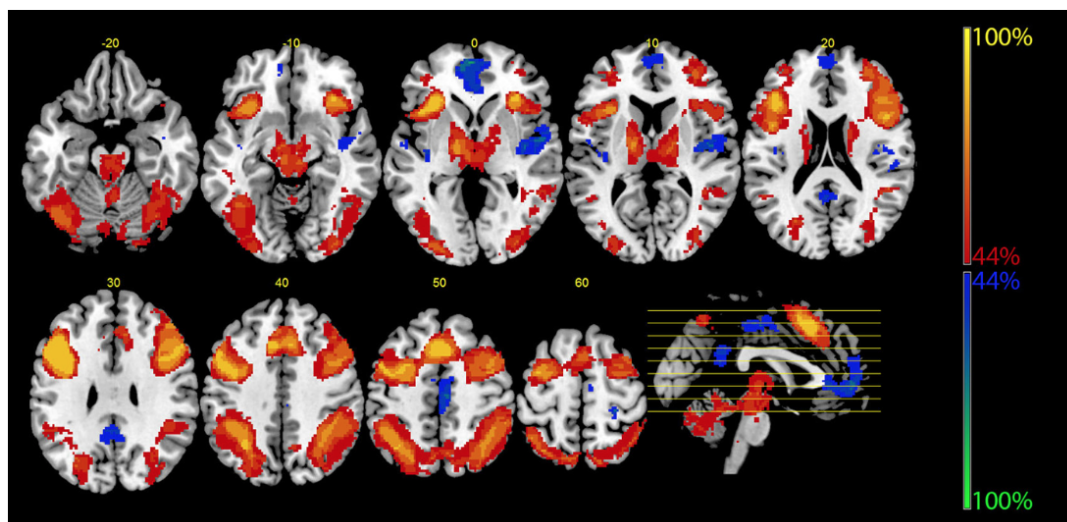


Figure 1. The figure shows probability maps for significant activation and deactivation across studies reported in Hugdahl et al. 2015 i.e. Extrinsic Mode Network (EMN) in red/orange and Default Mode Network (DMN) in blue.

2.2 The Default Mode Network (DMN)

Resting-state fMRI studies have allowed researchers to characterize the large-scale organization of neural networks via the analysis of temporally correlated BOLD-signal (Biswal, et al. 1995). In the absence of any external stimuli or instruction, the brain has been shown to have a unique activation pattern (Raichle 2015; Shulman, et al. 1997; Raichle et al. 2001). This resting activation has been termed the Default Mode Network (DMN) and includes parts of the subgenual anterior cingulate cortex, posterior cingulate cortex, the precuneus, lateral parietal cortex, medial prefrontal cortex, inferior temporal gyrus, parahippocampal gyrus, and the frontal pole/superior frontal cortex (Shulman, et al. 1997) (see figure 1). External stimuli or instructions will usually drive task-specific deactivations in the DMN, which is anti-correlated with the task related networks (Raichle 2010; 2015). Thus the term “default mode” denotes the brain’s default, or baseline state. It is presumed that during the resting state subjects experience an on-going state of conscious awareness largely filled with stimulus-independent thoughts (Qin and Northoff 2011) or mind wandering (Fox, et al. 2015). The DMN is hypothesized to perform functions such as self-referential activities (Northoff and Bermpohl 2004), self-inspection, and emotion regulation (Qin and Northoff 2011), the role of which diminishes during traditional cognitive tasks (Fox, et al. 2005). Furthermore, these functions are believed to be in opposition to externally orientated goal-directed cognition (Anticevic, et al. 2012). There is also emerging evidence that the DMN is associated with interoception and emotional awareness (Smith, et al. 2017; Wiebking, et al. 2011) although viscerosensory representation may be more associated with anterior insula and cingulate activity.

2.3 Network interactions

A considerable body of evidence has accumulated over recent years on the function of the DMN. This set of functions seems to be anti-correlated with oriented goal directed thought supported by the EMN. Here, we focus on DMN suppression and interaction with EMN (since EMN is considered up-regulated to such extrinsic goal-directed cognitive activity) and its functional role in health and disease. Collectively, research has shown that lower DMN activity is associated with better cognitive performance across a range of tasks (similar to those tasks described above; see (Anticevic, et al. 2012; Daselaar, et al. 2004), although some functional heterogeneity is likely (Leech, et al. 2011). This finding highlights the functional relevance of DMN suppression for goal-directed cognition, possibly by reducing ‘distracting’ goal-irrelevant functions supported by the DMN (e.g. mind-wandering or self-referential processing), and illustrates the functional significance of DMN suppression. This activation/deactivation dichotomy which is routinely observed in response to attention demanding tasks is also represented intrinsically in the resting human brain, demonstrable in the absence of any overt task or behaviour i.e. spontaneous fluctuations within a network and anti-correlations between networks (Fox, et al. 2005). Anticorrelations in these two opposing networks provide a context in which to understand brain function and suggest that both task-driven neuronal responses and behaviour are reflections of dynamic processes and organization in the brain (Sylvester, et al. 2012; Hugdahl, et al. 2015). Such states of network interaction are likely to be important for emotion and cognitive regulation (Anticevic, et al. 2012). Furthermore, group differences in the capacity to suppress the DMN may also be meaningful. For example, older adults exhibit deficits in filtering external distraction (Gazzaley, et al. 2008; Gazzaley and D'Esposito 2007) and less ability to suppress the

DMN during cognitive tasks (Buckner, et al. 2008). The ability to suppress DMN activation may be related to cognitive control ability (Leech, et al. 2011) and there is evidence that personality dimensions such as trait anxiety and worry may influence DMN connectivity (Forster, et al. 2015). Moreover, altered EMN/DMN interactions are also observed in psychiatric conditions.

3. Psychopathology and network dynamics

Several decades of brain imaging studies in psychiatric populations have produced an enormous body of work that reports a myriad of functional and anatomical brain alterations associated with a range of psychiatric disorders. Whilst neuroimaging studies in psychiatric populations have attempted to establish diagnosis- specific brain alterations e.g. hypofrontality in schizophrenia (Weinberger, et al. 1986) a recent meta-analysis of over 500 functional brain imaging studies across several diagnoses found that whole brain studies were not able to identify specific functional effects of diagnosis (Sprooten, et al. 2017) a finding that supports the new dogma that psychiatric diagnoses are not entirely separate entities. Indeed, given that varying degrees of cognitive impairment and emotional dysregulation are common across psychiatric disorders, it is likely that common pathophysiological elements exist. Dysfunction in limbic, hippocampal and prefrontal circuits may be a common and overlapping substrate of psychiatric pathophysiology (Godsil, et al. 2013). Accordingly, volumetric alterations in these circuits have been reported across a range of psychiatric diagnoses in patients with high levels of childhood trauma (Paquola, et al. 2016), suggesting that anatomical changes in these regions are at least partly related to a common antecedent to psychiatric diagnoses, rather than to the diagnoses themselves. Functionally, brain network connections and hubs have been shown to be

abnormal across many brain disorders (Crossley, et al. 2013) implicating network dysfunction as a common feature associated with psychopathology. Collectively, there appears to be mounting evidence that several psychiatric conditions have overlapping neural phenotypes, suggestive of common deficits at a systems level; these common pathophysiological features may manifest in brain network dysfunction and altered network interactions. It is well established that altered neural activation in DMN is associated with psychiatric conditions, and that reduced DMN suppression may represent a mechanism whereby cognitive deficits and symptoms are induced or exacerbated in psychiatric illnesses (Anticevic, et al. 2012; 2013). However, less is understood about how dysfunctional network interactions are related to underlying excitatory/inhibitory neurotransmitter function, which is also known to be altered across a range of psychiatric illnesses (Marin 2012). Here we will review evidence of network dysfunction across common psychiatric disorders i.e. schizophrenia, anxiety and Major Depressive Disorder.

3.1 Schizophrenia

Schizophrenia is a severe and debilitating mental illness characterized by psychotic symptoms (hallucinations and delusions), negative symptoms and wide-ranging cognitive deficits (Green 1998). In particular, impaired executive functioning (i.e. inhibition, updating and set-shifting) is most widely observed in patients with schizophrenia and is consistently associated with impaired function of the prefrontal cortex e.g. (Weinberger, et al. 1986). Minzenberg and colleagues (Minzenberg, et al. 2009) examined if a ‘cognitive control network’ (analogous to the EMN) exhibited alerted activity across functional neuroimaging studies of executive cognition in schizophrenia (i.e. working memory, attention and interference tasks). Healthy

controls and schizophrenia patients activated a similar network including the DLPFC, ventrolateral prefrontal cortex, anterior cingulate cortex, and thalamus. However, patients showed reduced activation in this cognitive control network and significantly, increased activation was observed in midline cortical areas; regions within the DMN. These findings are consistent with the view that executive function deficits in schizophrenia may be associated with aberrant DMN activation (lack of suppression during demanding tasks) in schizophrenia e.g. (Nygard, et al. 2012; Razavi, et al. 2013) and with altered network dynamics between cognitive control and default mode networks. Hugdahl and colleagues (Hugdahl, et al. 2009a; Hugdahl, et al. 2009b) suggest that the cognitive impairment and hypo-activation seen in schizophrenia patients when exposed to challenging cognitive tasks could be caused by failure of interactive regulation between the DMN and EMN networks, rather than a deficit with regard to a specific brain region. In other words, in order for any goal-directed activity to be up-regulated, default mode activity has to be correspondingly suppressed or down-regulated, and that schizophrenia patients show increased sustained activation in the posterior parts of the DMN during tasks (Kindler, et al. 2015).

Altered network dynamics have also been associated with specific psychotic symptoms. Northoff and Qin (2011) propose that hallucinations in schizophrenia may be caused by aberrant resting state activity in the DMN and in the auditory cortex, possibly explaining the often self-reflective nature of auditory hallucinations. Neuroimaging studies have reported altered DMN activity and connectivity in schizophrenia patients with hallucinations. A study by Jardri and colleagues (Jardri, et al. 2013) used fMRI to ‘capture’ neural activity during hallucinations in adolescents

with a brief psychotic disorder. Whilst, primary-sensory-cortex activity was shown to be associated with increased vividness of the hallucinatory experiences, disengagement of the DMN was concomitant with hallucinations. Leroy and colleagues (Leroy, et al. 2017) have recently replicated this finding and also report spatial and temporal instabilities of the DMN correlated with the severity of hallucinations. These results suggest that hallucinatory experiences emerge from a spontaneous DMN withdrawal. Furthermore, Lefebvre and colleagues (Lefebvre, et al. 2016) report that ignition and extinction of the hallucinatory experiences are associated with different interactions within resting-state networks: notably that ignition is associated with fluctuations of the hippocampal complex that may trigger the DMN withdrawal, and that the end of the experience is associated with a ‘take-over’ of the EMN regions (over the DMN). Such findings may be compatible with the view that a failure of inhibition and attentional focus, mediated via top-down control, contribute to the hallucinatory experience (Waters, et al. 2012) i.e. hallucinations accompany hyper activation in sensory region that is not inhibited, due to impaired prefrontal function. Although speculative, it is possible that increased activity in prefrontal region during cessation of hallucinations is a consequence of restored EMN/DMN balance. However, it should be noted that Lefort-Besnard and colleagues (Lefort-Besnard, et al. 2018) report in a large cohort of patients with schizophrenia (using data-derived network atlases and multivariate pattern-learning algorithms) that the DMN was not the primary driver of brain dysfunction in schizophrenia. Instead, functional and structural aberrations were frequently located outside of the DMN.

3.2 Anxiety, trait anxiety and affective disorders

Anxiety disorders defined by excess worry, hyperarousal and debilitating fear are some of the most common psychiatric conditions in the world and have an estimated

lifetime prevalence of 14.3% (Kessler, et al. 2005). Furthermore, trait anxiety is part of the ‘normally distributed’ personality dimension of neuroticism and describes proneness to negative emotions, especially fears, worries and anxiety (Berggren and Derakshan 2013a, 2013b). The effects of anxiety and trait anxiety on cognitive performance have long been recognised (Berggren and Derakshan 2013a, 2013b). Neurocognitive models have focused on how anxiety can affect cognitive control and how this effect is mediated by brain mechanisms (Braver 2012; Eysenck, et al. 2007; Forster, et al. 2015; Sylvester, et al. 2012). There is considerable evidence from neuroimaging studies that anxiety affects (usually increases) task-related activity in fronto-parietal and cingulo-opercular networks (Basten, et al. 2012; Basten, et al. 2011; Sylvester, et al. 2012). Precisely how activity in these networks is effected by anxiety may depend on the demands of the task being undertaken however (Berggren and Derakshan 2013a, 2013b), i.e., tasks requiring executive control may lead to *inefficient* neural processing and/or the need for increased compensatory activation in people with high levels of anxiety (Eysenck, et al. 2007). Moreover, experimental work has shown that anxious individuals exhibit more mind wandering than low-anxious individuals during cognitive tasks (Robison, et al. 2017). Recently, studies have begun to investigate how anxiety affects resting state activity in the DMN us fMRI. There is evidence that worry, a cognitive component of trait anxiety (Gros, et al. 2007), and mind wandering both involve the DMN (Fox, et al. 2015), and that anxiety and worry are associated with increased DMN activation (Servaas, et al. 2014). Gentili and colleague (Gentili, et al. 2015) found DMN activity was correlated positively with social anxiety and Maresh and colleagues (Maresh, et al. 2014) found higher levels of social anxiety were positively associated with DMN activity during task performance. In addition to these correlational studies, Pletzer and colleagues

(Pletzer, et al. 2015) found less deactivation in DMN areas during task performance for those high in math anxiety. However, not all brain-imaging findings are directly compatible with the prediction of relatively increased DMN activity in people with high trait anxiety. Fales and colleagues (Fales, et al. 2008) found increased deactivation of DMN in high-anxious individuals during a working memory task. Whilst the exact relationship between DMN activity and anxiety/worry is unclear, it appears that anxiety is associated with altered activity in this network. Task-related deactivation of DMN may depend to some extent on the type of task and its reliance upon executive processes (Eysenck, et al. 2007). Whilst the studies outlined above provide evidence for altered EMN and DMN activation in anxious individuals, it is unclear how anxiety affects interactions between these networks. It has been shown, however, that anxious individuals can maintain effective task performance when goal-directed attentional control is compromised, via increased compensatory activation in the dorsal anterior cingulate (Braver 2012; Braver, et al. 2009).

Cognitive impairment across a range of tasks is also reported in people with depression (see Bora, et al. 2013) and similar to studies in anxious cohorts, altered network connectivity has also been reported in depression. Brakowski, et al. (2017) reports that disrupted network connectivity has been found in the DMN, the central executive network region (analogous to the EMN), and the salience network in major depression disorder (MDD) cohorts. Both decreased and increased DMN activity and connectivity has been reported in MDD groups (Brakowski, et al. 2017, Zhang, et al. 2016) and may be linked to negative rumination (Lemogne, et al. 2010). In particular, a failure to suppress DMN nodes has been linked to negative internal thought rather than cognitive impairment (Anticevic, et al. 2012). As such, rather than cognitive

impairment in MDD being related to a primary inability to engage executive resources, a hyperactive DMN in depression may have detrimental effects on cognitive performance (Rose, et al. 2006) even if the primary abnormality is not with cognitive control networks or the EMN. Pharmacological and psychological treatments for MDD alter functional connectivity throughout multiple brain regions notably the DMN and EMN regions (Brakowski, et al. 2017).

3.3 Intermediate summary

The research discussed above suggests that functional activation and connectivity in the DMN is altered in schizophrenia, anxiety and depression and that altered DMN interactions with EMN regions may impair cognition. However, differences in the precise nature of DMN/EMN interactions in schizophrenia, anxiety and MDD may explain the range and severity of cognitive impairments and emergence of other symptoms seen across these different psychiatric diagnoses. For example, in people with anxiety, altered DMN/EMN interactions may result in inefficient cognitive control than can be ‘masked’ to some extent by compensatory processes. This is because worry and mind wandering are associated with increased DMN activity and connectivity that may compete for limited neural resources (Eysenck and Calvo 1992) in EMN during cognitive tasks (Barker, et al. 2018). This may consequently affect cognitive function, depending on the level of executive function required by the task. Consistent with this view, Bishop (Bishop 2009) reports that DLPFC activation is negatively associated with trait anxiety scores at low cognitive loads. However, when greater executive control is required people with high levels of trait anxiety can engage compensatory or reactive control networks i.e. anterior cingulate activity (Moser, et al. 2013) that allows *effective* behavioural performance to be maintained,

albeit *inefficiently* (Eysenck, et al. 2007). In patients with schizophrenia, however, it is possible that compensatory mechanisms are more difficult to deploy and consequently cognitive impairments are generally more severe than those seen in people with anxiety. For example, in patients with schizophrenia, there is a large literature reporting reduced engagement of the anterior cingulate cortex, a region involved in error monitoring (Carter, et al. 2001; Palaniyappan and Liddle 2012) that may be important for reactive cognitive control (Braver 2012). Hence, reduced engagement of EMN regions (particularly the DLPFC and inferior parietal cortex), commonly reported in schizophrenia cohorts, may result in demonstrable cognitive impairment due to a reduced capacity to engage ‘effective’ compensatory mechanisms. In patients with depression, cognitive impairment may be due to DMN over-activity to heightened rumination (Lemogne, et al. 2010), even in the absence of a primary cognitive deficit (possibly akin to heightened worry in anxious people). Whilst, the effects of DMN over-activity on EMN engagement and cognitive function in people with depression may be similar to those in anxious cohorts, it is less clear what, if any, compensatory neural mechanisms can be deployed by depressed patients to maintain effective behavioural performance. Thus, whilst impaired DMN suppression may be observed across different psychiatric diagnoses, the net effects on cognition would depend on the precise nature of the DMN’s interaction with other brain networks, particularly EMN regions. One study has explicitly examined transdiagnostic changes in resting state (DMN and EMN regions) functional connectivity in patients with schizophrenia and depression. Schilbach and colleagues (Schilbach, et al. 2015) report common dysconnectivity patterns as indexed by a significant reduction of functional connectivity between precuneus (a DMN region) and bilateral superior parietal lobe (an EMN region) in schizophrenia and depression.

However, diagnosis-specific connectivity reductions of the operculum in schizophrenia are seen relative to depression. Given the operculum's role in somatosensory integration, diagnosis-specific connectivity reductions may indicate a pathophysiological mechanism for basic self-disturbances that are characteristic of schizophrenia, but not depression (Schilbach, et al. 2015).

4. Network interactions and excitatory/inhibitory neurotransmitter balance

As outlined earlier, there exists an anti-correlated relationship in networks involved in extrinsic cognitive control, and internally focused processes (Fox, et al. 2005; Raichle 2015), a relationship that is perturbed in psychiatric conditions (Anticevic, et al. 2012; Jardri, et al. 2013; Sylvestor, et al. 2012; Brakowski, et al. 2017). Dynamic relationships between these networks are likely mediated at a synaptic level by excitatory/inhibitor neurotransmission (Hugdahl and Sommer 2018). An important question therefore is ‘how underlying neurotransmitter mechanisms modulate regions within major brain networks such as the DMN and EMN’? The brain’s main excitatory and inhibitory neurotransmitters, glutamate and *gamma*-Aminobutyric acid (GABA) respectively, are important for maintaining a precise excitatory-to-inhibitory (E/I) balance within the brain (Deneve and Machens 2016), which is particularly important for the maintenance of stable network dynamics (Carcea and Froemke 2013). Changes in neuronal activation at network levels, must have a corresponding change at the receptor and neurotransmitter level that causes the neurons to alter their firing rate (see Hugdahl and Sommer 2018 for discussion). Computationally it has been showed that disruption of E/I balance in favour of excitation causes aberrant inferences in hierarchical networks (Jardri and Deneve 2013); for example the

amplification of feed-forward messages correlates with hallucinations and delusions severity in schizophrenia patients (Jardri, et al. 2018).

It has been proposed that the reciprocal relationship between networks such as the EMN and DMN is mediated via ‘net inhibitory long-range projections’ and that local disinhibition renders DMN hyperactive and less sensitive to long-range suppression (Anticevic, et al. 2015; Hayden, et al. 2009) potentially disrupting EMN/DMN interactions. The increasing use of ¹H-MRS together with Blood Oxygen Level Dependent (BOLD)-fMRI measures allows for quantification of levels of brain glutamate and GABA, and how they relate to activity in cortical and subcortical networks. A seminal study using ¹H-MRS and functional MRI by Falkenberg and colleagues (Falkenberg, et al. 2012) report that resting glutamate levels in the dorsal ACC (a key hub in cognitive control networks) predicts the strength of the functional activity during a cognitive control task. This relationship was observed in the retrosplenial cortex, the orbitofrontal cortex, the inferior parietal lobe, all regions within the DMN. A systematic review of ¹H-MRS-fMRI multimodal imaging studies reporting effects of glutamate and GABA on network activation is provided by Duncan and colleagues (Duncan, et al. 2014). ¹H-MRS-fMRI multimodal imaging studies in psychiatric and psychiatric risk populations are listed in Table 1.

Glutamate transmission can also be experimentally mediated by the N-methyl-d-aspartate (NMDA) receptor antagonist ketamine. Anticevic and colleagues (Anticevic, et al. 2015) showed that administration of ketamine disrupted the reciprocal relationship between anticorrelated networks (i.e. DMN and task positive networks). The degree of this disruption predicted working memory task performance and transiently evoked symptoms characteristic of schizophrenia. Furthermore, prefrontal

cortex hyper-connectivity in healthy volunteers who were administered ketamine resembles prefrontal cortex connectivity patterns seen in individuals at high risk for schizophrenia and patients in the early phase of the illness (Anticevic, et al. 2013; 2015). These findings highlight the role that glutamate and NMDA receptors play in modulating intrinsic and extrinsic networks and subsequent cognitive control. Regarding inhibitory neurotransmission, a recent meta-analysis of ¹H-MRS studies investigating GABA levels across psychiatric conditions (Schur, et al. 2016) report reduced GABA levels in symptomatic depressed patients and in patients with schizophrenia relative to healthy controls. These findings provide further support for E/I neurotransmitter imbalance in MDD and schizophrenia, supported by more recent studies which all report aberrant metabolite levels in schizophrenia and psychosis (Dwyer, et al. 2018; Jelen, et al. 2018; Psomiades, et al. 2018; Reid, et al. 2019; Kim, et al. 2018; Singh, et al. 2018). However, currently there is no evidence for differences in GABA levels between healthy controls and patients with bipolar or anxiety disorders (Schur, et al. 2016).

¹H-MRS studies in patients with schizophrenia and individuals at clinical high risk (CHR) for psychosis have also shown that glutamate concentrations are associated with aberrant activation in cognitive control networks. Falkenberg, et al. (2014) report that in patients with schizophrenia, there is a positive association between ACC glutamate levels and activation in the bilateral inferior parietal lobe during a cognitive control task, opposite to that seen in healthy controls. Using ACC Glx (a combined measure of glutamate and glutamine), Cadena, et al. (2018) report similar findings of an altered relationship between glutamatergic metabolites and BOLD in cognitive control regions in schizophrenia patients that change after six-weeks of medication.

Fusar-Poli and colleagues (Fusar-Poli, et al. 2011) report that during a verbal fluency task (requiring executive control), CHR subjects showed greater activation than healthy volunteers in the bilateral middle frontal gyrus. Thalamic glutamate concentrations were lower in the CHR than in healthy volunteers and were negatively associated with activation in prefrontal and left orbitofrontal cortex regions. These findings suggest that psychosis risk is associated with a perturbed relationship between subcortical glutamate concentrations and task related activity in EMN/DMN regions. Furthermore, Allen and colleagues (Allen, et al. 2015) report that reduced thalamic glutamate concentrations are associated with poor functional outcome in a CHR group; a relationship mediated by perturbed activation in medial prefrontal regions during an executive task. In the hippocampus (part of the DMN) glutamate concentrations have also been shown to predict local activation during a word memory task, an association that appears to be absent in a CHR cohort (Valli, et al. 2011).

TABLE 1 HERE

Taken together, these findings suggest that glutamate is crucial for functioning in networks important for cognitive control. However, in both of these CHR studies neither cortical glutamate nor GABA concentration were assessed, so hypotheses relating to altered E/I balance in regions associated with EMN/DMN could not be directly tested. Whilst, increased cortical glutamate and Glx levels have been reported in a small CHR cohort (Liemburg, et al. 2016), the complex dynamics between EMN/DMN and how these may be perturbed in CHR cohorts due to E/I neurotransmitter imbalances is yet to be fully examined. In addition to cognitive impairment in CHR cohorts, aberrant beliefs or percepts, coincidence detections and

feeling of strangeness are common experiences in the prodromal phase of psychosis (Nelson, et al. 2009). Interestingly, the perturbation of NMDA receptor function using antagonists such as ketamine can results in these experiences and has been proposed to result from disruptions in the E/I balance in cortical microcircuitry (Deneve and Machens 2016).

Altered glutamate levels and E/I imbalance may also underlie the experience of hallucinations in people with schizophrenia. The BOLD response derived from fMRI experiments can be viewed as an indirect marker of neuronal metabolic turnover, which in turn would be related to glutamate transmission (Hugdahl, et al. 2015; Jardri, et al. 2016). A well-established observation during the experience of hallucinations is spontaneous activation in sensory cortices e.g. the speech sensitive auditory cortex during auditory verbal hallucinations (Allen, et al. 2008; Allen, et al. 2012; Jardri, et al. 2011). It has been proposed that spontaneous elevations in glutamate transmission could initiate hallucinatory episodes, which in turn could explain the spontaneous activation increase during hallucinations (Kompus, et al. 2011). Consistent with the notion of an E/I imbalance as a precipitating mechanism for hallucinations (Jardri, et al. 2016), metabolic changes in speech-related areas have been widely reported in functional brain imaging studies of schizophrenia patients with hallucinations (Ford, et al. 2012; Homan, et al. 2013). To test this hypothesis, Hugdahl and colleagues (Hugdahl, et al. 2015) used MR spectroscopy to measure cortical Glx levels, and found increased Glx levels in fronto-temporal regions in patients with auditory hallucinations relative to patients without AVH. Furthermore, Glx levels are also elevated in patients with a history of lifetime hallucinations as compared to patients without (Curcic-Blake, et al. 2017a).

It is also reported that hallucinations are associated with impaired connectivity of large-scale networks at both functional (Alderson-Day, et al. 2015) and structural levels (Geoffroy, et al. 2014). Functional connectivity between Wernicke's area and Broca's areas, for example, is disrupted during inner-speech processing in schizophrenia patients who hear voices (Curcio-Blake, et al. 2017a). Studies conducted in schizophrenia patients suggest that network dysconnectivity may in part be due to impaired control of synaptic plasticity (Friston and Frith 1995) notably of NMDA receptor dysfunction (Stephan, et al. 2009) and cortical disinhibition due to increased glutamate function (Stephan, et al. 2006). Meta-analysis of ¹H-MRS in schizophrenia patients however, suggested that illness phases are associated with different glutamate profiles, both increased and decreased, and suggests a more complex picture (Marsman, et al. 2013; Merritt, et al. 2016).

Hallucinations may also be related to reduced inhibition due to impaired prefrontal control or hierarchical control (Waters, et al. 2012). Since long-range connections in the brain are overwhelmingly excitatory (Jardri and Deneve 2013), inhibitory messages may be 'perturbed', and excitatory signalling, if not controlled by the presence of equivalently strong inhibitory signalling, might become dysfunctional. There are very few studies however that have examined GABAergic concentrations in schizophrenia (Egerton, et al. 2017) and none that have specifically focused on patients with hallucinations. Regarding other disorders, there is currently a paucity of multimodal neuroimaging studies examining how network interactions are mediated by E/I neurotransmission in people with anxiety and affective disorders. However, a small number of multimodal imaging studies in psychiatric and psychiatric risk groups report altered associations between cortical glutamate and GABA concentrations and activity and connectivity in EMN and DMN regions in MDD

patients (Horn, et al. 2010; Deligiannidis, et al. 2018; Zhang, et al. 2016), childhood trauma (Duncan, et al. 2015) and depression risk cohorts (Wiebking, et al. 2014).

¹H-MRS studies have shown that anterior cingulate glutamate levels can predict anxiety severity (Modi, et al. 2014) and there are a number of studies reporting that MDD is associated with state dependent down-regulation of glutamate concentrations in the anterior cingulate cortex (see Luykx, et al. 2012; Lener, et al. 2017). However, studies of GABA in MDD patients have largely produced discepent findings although the most replicated finding is an overall reduction in GABA in the occipital lobe (Price, et al. 2009; Sanacora, et al. 2004). One multimodal (fMRI and ¹H-MRS) has shown, that relative to people with low trait anxiety, people with high trait anxiety have an altered relationship between prefrontal cortex activity and glutamate levels during a cognitive control task (Morgenroth, et al. 2018). Interactions with DMN regions were not examined, however.

5. Effects of Trauma and Stress on E/I balance and network dynamics

Trauma, particularly early trauma, is a well-established risk factor for psychiatric disorders (Paus, et al. 2008). Exposure to environmental risk factors for psychiatric illness, such as trauma, may be especially influential during developmentally sensitive periods such as childhood and adolescence when brain maturation is on-going (van Os, et al. 2010). However, the mechanism through which trauma in childhood affects brain development, and increases risk for psychiatric illness in adulthood remains only partly understood. It has been proposed that early trauma can lead to ‘stress sensitization’ (Gomes and Grace 2017) and recent work has shown alterations in methylation of genomic areas responsible for the stress response (Houtepen, et al.

2016; Adams, et al. 2016). However, the exact mechanisms via which these changes affect brain function and structure remains to be studied. One approach that can be used to address this issue is to examine the relationship between neuroimaging findings in adults with psychiatric diagnoses, and a measure of the extent to which they experienced trauma in childhood. Studies using this approach report altered structure (Paquola, et al. 2016) and function (Teicher, et al. 2016) in a range of regions including the prefrontal cortex, crucial for cognitive function, and also part of the EMN. Neurocognitive data are consistent with these functional findings, with a range of cognitive deficits observed in childhood trauma cohorts (DePrince, et al. 2009; Pechtel and Pizzagalli 2011).

Neurofunctionally, psychiatric patients with a history of childhood abuse, display reduced activation in left inferior and dorsolateral prefrontal cortex relative to the healthy and psychiatric controls during tasks requiring executive control (Lim, et al. 2016). Severe childhood abuse is also associated with abnormally increased activation in prefrontal regions during an interference task (Lim, et al. 2015), similar to that seen in anxious cohorts (Sylvester, et al. 2012). At a network level, there is evidence that childhood abuse is associated with decreased functional connectivity in fronto-parietal attention networks although this may be partly determined by genotype (Hart, et al. 2017). Taken together, these functional imaging findings suggest that during cognitive tasks, activation and connectivity in EMN regions is affected by childhood trauma, however, how these functional changes in EMN regions are related to changes in DMN activity is unclear.

Emerging evidence suggests that early trauma and maltreatment can also affect the development of sensory systems and functional networks responsible for emotional

regulation (Teicher, et al. 2016). Sensory systems are particularly susceptible to experience-dependent plastic response (Takesian and Hensch 2013). Voxel based morphometry analysis of MRI scans of young adults show that episodes of parental verbal abuse during childhood were associated with differences in grey matter density in the primary auditory cortex within the superior temporal gyrus (Tomoda, et al. 2011). Intriguingly, given the strong association between childhood trauma and verbal hallucinations in adulthood (Read, et al. 2005), differences were also seen in language processing pathways that connect speech motor and sensory regions (Choi, et al. 2009); a network implicated in the experience of auditory hallucinations (Allen, et al. 2008; Allen, et al. 2012). Childhood abuse has also been reported to be associated with altered grey matter volume in visual processing areas (Tomoda, et al. 2011).

With regards to EMN/DMN interactions, childhood trauma may affect the development of functional network architecture. Teicher and colleagues (Teicher, et al. 2016) report that in maltreated individuals, centrality (a measure of a given neural regions network integration derived from graph theory) was reduced in the left ACC, temporal pole and middle frontal gyrus and was increased in the anterior insula and precuneus, regions within EMN/DMN. Increased centrality in the precuneus in maltreated individuals is particularly interesting as this region is a key hub in the DMN and may be a critical for self-referential thinking/processes (Northoff and Bermpohl 2004) possibly linked to rumination and worry. Teicher and colleagues speculate that increased precuneus centrality in maltreated individuals may be analogous to the enhanced functional connectivity within precuneus based posterior DMN in patients with depression (Li, et al. 2013), who often have histories of maltreatment. Indeed, there is a growing body of research linking childhood trauma to decreased DMN connectivity and increased DMN activity during cognitive tasks

(Philip, et al. 2013; Sripada, et al. 2014), similar to the activation and connectivity patterns observed in people with psychiatric conditions.

However, the mechanisms through which childhood trauma and maltreatment affect anatomy, function and connectivity within DMN, EMN and in regions involved in sensory processing are largely unknown. Work in experimental animals has revealed that stress sensitization and increased stress responsivity, due to adverse adolescent environments, can disrupt prefrontal activity (Gomes and Grace 2017; Gomes, et al. 2016). In particular, the medial prefrontal cortex, a key region of the DMN, is a region known to be involved in regulating stress responses (Rosenkranz and Grace 2002). Medial PFC dysfunction can increase the vulnerability to stress in terms of changes in the dopamine system (Gomes, et al. 2016), potentially increasing risk for psychosis and affective disorders. Heightened stress responsivity in rodents is also reported to lead to parvalbumin loss in GABAergic interneurons (Gomes, et al. 2016), which in turn may affect E/I neurotransmitter balance. There are few studies in humans that examine the relationship between early trauma and cortical glutamate and/or GABA concentrations. Duncan and colleagues (Duncan, et al. 2015) report that in non-psychiatric adults that have experienced childhood trauma, increased glutamate concentrations in the medial PFC mediate BOLD response to adverse stimuli in a network including the insula and motor cortex. Although not specifically in a childhood trauma cohort, a recent study in patients with post-traumatic stress disorder (Harnett, et al. 2017) reports that within dorsal ACC there was a positive linear relationship between Glx concentrations (combined Glutamate and Glutamine concentrations) and current stress disorder symptoms. Further, Glx concentrations showed a positive linear relationship with future stress disorder symptoms (i.e., assessed 3 months post-trauma). Experimentally induced stress, using

cholecystokinin-tetrapeptide (CCK-4), significantly increased glutamine concentrations in the ACC suggesting that disturbances in inhibitory-excitatory equilibrium may be related to stress and panic (Zwanzger, et al. 2013). Recently it has been shown that intrusive memories, images and hallucinations (all symptoms of psychiatric disorders) can be controlled by GABAergic inhibition. Schmitz and colleagues (Schmitz, et al. 2017) report that GABAergic inhibition of hippocampal retrieval activity forms a key link in a fronto-hippocampal inhibitory control pathway underlying thought suppression. Finally, and although only an indirect measure of excitatory neurotransmitter function, hippocampal and prefrontal cortex resting cerebral blood flow changes in people at CHR for psychosis, have been shown to be related to levels of childhood trauma (Allen, et al. 2017).

These findings suggest that altered prefrontal glutamate, glutamine concentrations and GABA concentrations may play a role in psychiatric (or psychiatric like) symptoms following a traumatic experience. In particular, the relationship between early traumatic experiences and vulnerability to psychiatric conditions such as schizophrenia may be mediated via E/I neurotransmitter imbalance, disinhibition and impaired EMN/DMN interactions. However, much more work is needed to establish these relationships in humans.

6. Summary, conclusions and future research

We have discussed the functional importance of EMN/DMN dynamics and how altered or inefficient interactions between these networks may underlie impaired cognition and symptoms (i.e. hallucinations) across psychiatric conditions. Currently, there is substantial evidence of altered engagement of EMN and DMN in the

psychiatric conditions i.e. schizophrenia, anxiety and depression. However, there are fewer studies that have explicitly examined the dynamics of EMN/DMN activation and/or connectivity in psychiatric populations, and how altered network interaction may affect cognition. Moreover, although altered EMN/DMN interactions are likely to be central to cognitive changes in psychiatric conditions, the precise nature of the network alterations appears to be different in different disorders. More research is also needed to establish the neuropharmacology of EMN/DMN dynamics. Whilst there is clearly a relationship between EMN/DMN activity and excitatory signalling, the exact nature of this relationship is poorly understood. Further, how changes in excitatory and inhibitory signalling and glutamatergic and GABAergic concentrations impact on the E/I neurotransmitter balance and EMN/DMN interactions needs to be researched in greater depth. The increased use of MR spectroscopy together with BOLD-fMRI recordings will allow for a better understanding of how brain metabolites and transmitters are related to network activation. Finally, there is a burgeoning literature relating early traumatic experiences, a major antecedent of adult psychiatric disorders, to altered function in EMN/DMN regions and sensory regions known to be important for cognition and sensory processing. Taken together, the research and findings discussed here lead towards a plausible mechanistic hypothesis, linking early traumatic experiences to cognitive dysfunction and symptoms mediated by E/I neurotransmitter imbalances.

6.1 Limitations and Future work

A potential limitation with the approach suggested here is that fMRI-BOLD and MRS metabolites typically are acquired separately, with minutes between the signal uptakes. This creates a problem when interpreting changes in E/I neurotransmitter balance and

relation to DMN/EMN network interactions. Recent progress in MR spectroscopy methods may be able to overcome these technical obstacles, where it will be possible not only to acquire glutamate and GABA approximately simultaneously, but also simultaneous BOLD-fMRI and MRS acquisitions. A second limitation is that we do not discuss here recent and promising findings of a relationship between inflammation and the immune system and psychosis (Khandaker, et al. 2015). Immune response changes, due to stressful life events, may have implications for an understanding of network dynamics and underlying transmitter balance. In particular, there is now broad acceptance that psychosis related volumetric and functional changes in hippocampus, a key DMN region, are related to an inflammatory response from an aberrant immune system (Kim, et al. 2016). We see this line of research, bringing together all of these modalities, as potentially important in future work. If a link between network dynamics and transmitter balance can be established, this can have implications for development of new intervention strategies, with more targeted treatments, aimed at restoring functional dynamics and neurotransmitter balance.

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Reference	MRS-fMRI	Diagnosis	Sample	Findings
Falkenberg et al. (2014)	MRS: ACC Glu fMRI: auditory cognitive control task	Schizophrenia (SCZ)	17 SCZ 17 HC	SCZ: (+) between ACC Glu and BOLD in L/R IPL HC: (-) between ACC Glu in L/R IPL
Cadena et al. 2018	MRS: ACC Glx/Cr fMRI: Stroop Task	SCZ	22 SCZ (scanned twice) 20 HC	SCZ (baseline): (-) between Glx/Cr and BOLD in ACC, ins, prec, PCC HC (baseline): (+) between Glx/Cr and ACC, Ins, prec, PCC.
Fusar-Poli et al. (2011)	MRS: Thalamic Glu fMRI: Verbal Fluency task (fMRI)	Psychosis Clinical High Risk (CHR)	24 CHR 17 HC	CHR: (-) between Thalamic Glu and BOLD in the R dorsolateral PFC/L OFC and (+) R hippocampus and L/R temporal cortex. HC: (-) between thalamic Glu in R/L PFC, R hippocampus and STG
Valli et al. (2011)	MRS: Hippocampal Glu fMRI: Word Memory Task	Psychosis CHR	22 CHR 14 HC	CHR: No correlation between hippocampal Glu and BOLD. HC: (+) between hippocampal Glu and MTL BOLD
Allen et al. (2015)	MRS: Thalamic Glu fMRI: Verbal Fluency Task	Psychosis CHR	33 CHR 27 HC	CHR (poor function): (-) between thalamic Glu and PFC/striatal BOLD CHR (good function) & HC: No correlation between thalamic Glu BOLD
Horn et al. (2010)	MRS: pgACC and left anterior Ins Glx fMRI: resting state functional connectivity	Major Depressive Disorder (MDD)	22 MDD 22 HC	MDD: (+) between Glx and resting-state functional connectivity (pgACC – anterior Ins). HC: No correlation between Glx and resting-state functional connectivity in PgACC and anterior Ins ROI
Wiebking et al. (2014)	MRS: L Ins GABA fMRI: introceptive-	Depressed Affect (Beck	24 HC	(+) between L Ins GABA and BOLD

	exteroceptive awareness task	Hopelessness Scale)		during interoceptive stimuli. GABA and interoceptive signal changes in the insula predicted the degree of depressed affect
Zhang et al. (2016)	MRS: Medial PFC glu and GABA fMRI: amplitude of low frequency fluctuations (ALFF) in resting state data (fMRI)	MDD	11 MDD (female) 11 HC (female)	MDD: (+) between medial PFC Glu and resting state ALFF (BOLD) HC: no correlation between medial PFC Glu and ALFF
Deligiannidis et al. (2018)	MRS: pgACC and occipital GABA/Cr fMRI: resting state functional connectivity (RSFC)	Post-partum depression (PPD)	45PPD 30HC	PPD: (+) between PgACC GABA/Cr and dorsomedial PFC-insula RSFC and occipital cortex GABA/Cr and dorsomedial PFC-amygdalae/parietal RSPC HC: As above
Duncan et al. (2015)	MRS: medial PFC Glu fMRI: resting state and adverse stimuli	Childhood Trauma (CHT)	12 HC	(+) between mPFC Glu and motor cortex/left insula BOLD during aversive stimuli associated with CHT scores
Morgenroth et al. (2019)	MRS: R medial PFC Glu fMRI: Stroop Task	Trait Anxiety (TA)	20 Low TA 19 High TA	Low TA: (+) between mPFC Glu and left dorsolateral PFC BOLD during incongruent trials High TA: no correlation between mPFC Glu and BOLD in dorsolateral PFC

Table 1: Multimodal imaging studies in in psychiatric/ risk populations

Abbreviations: MRS = 1H-Magnetic Resonance Spectroscopy. fMRI = Functional Magnetic Resonance Imaging, (+) = positive correlation, (-) = negative correlation, Glu = glutamate, Glx = glutamate/glutamine, Cr = creatine, L = left, R = Right, ACC = anterior cingulate, PFC = prefrontal cortex, IPL = interior parietal lobe, Ins = insula, prec = precuneus, PCC = posterior cingulate cortex, OFC = orbitofrontal cortex, STG = superior temporal gyrus, MTL = medial temporal lobe, pgACC = pregenual anterior cingulate cortex,